**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| App. No. | : | 10/820,656 | Confirmation No. 8010 |
| Applicants | : | David K. Gong, et al. | |
| Filed | : | April 8, 2004 | |
| TC/A.U. | : | 1616 | |
| Examiner | : | Alstrum-Acevedo, J.H. | |
| Docket No. | : | 31176282-004001 | |
| Customer No. | : | 51738 | |
| Entitled | : | Hemophilia Treatment by Inhalation of Coagulation Factors. | |

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Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

## REPLY BRIEF

Appellants filed the Appeal Brief on January 28, 2008, and an Amended Appeal Brief on March 20, 2008, in response to a final Office Action, dated October 26, 2007. An Examiner's Answer was filed on May 30, 2008, and the deadline to file a response is July 30, 2008. Therefore, the Reply Brief is timely filed.

This Reply Brief incorporates the text of the Amended Appeal Brief in its entirety. However, for brevity only the following salient reply points are made.

1. **ADMISSION OF MISSING ELEMENT**

Examiner admits that preventive treatment is absent. See Examiner's Answer, Page 13 ("Appellants are correct that the cited combined prior art **does not explicitly teach** (a) preventing hemophilic bleeding") (emphasis added). Examiner does not discuss 100 hr dosing, but as it is related to preventive treatment, it too is absent, and it is Applicants position that both are admitted to be absent from the teaching of the cited art.

A *prima facie* obviousness case is not made where elements are absent.

2. **UNEXPECTED RESULTS UNREBUTTED**

Examiner does not address Applicants assertion of "unexpected results." The assertions of unexpected results remain unrebutted.

3. **FACTUAL ERRORS**

a) Examiner states "Appellants have misread the cited prior art as teaching FIX formulations that necessarily comprise ethanol." Examiner's Reply, Page 13. Applicants have not stated this, and do not reply on such fact.

b) Examiner states that Gupta "teaches the intravenous bolus administration of FIX liquid formulations, is the closest prior art." Examiner's Reply, Page 20. This is incorrect. Gupta relates to pulmonary delivery of FIX.

c) Examiner states "Appellants have not provided competent 'head-to-head data' because Lechuga, not Gupta, is the closest prior art." Examiner's Reply, Page 20. This is incorrect. The invention is directed to **treatment** of hemophilia with FIX, not a formulation of FIX, and Applicants **directly** compared intravenous FIX treatment against inhaled FIX treatment in dogs (see Fig. 8).

d) Examiner presumes monomer content and activity based on FPF and MMAD (each about 3 microns):

> The Office's position regarding the required 90%+ FIX monomer content and 80%+ post-aerosolization activity, as stated above, is that because the

> inhalable FIX dry powder formulations invented by Lechuga are made from fine, unagglomerated, unaggregated spray dried aqueous formulations, as evidenced by the high emitted dose and MMAD of 2.7 microns and FIX exists as a single polypeptide in vivo, it is a reasonable conclusion that Lechuga's invented inhalable FIX dry powder formulations would have a greater than 90% FIX monomer content and 80% post-aerosolization activity.").

See Examiner's Reply, Page 17. However, the sizes in question are **orders of magnitude apart** (FIX is about 100 Angstroms[1] = 0.01 microns), and the micron size of a dry particle has **NO** relationship to activity. In fact, three hundred monomers or 150 dimers would each meet the required FPF and MMAD sizes! Thus, Examiners' assumption of monomer and activity level based on particle size[2] is factually unsupported and in error.

e) The Examiner states that "Examiner agrees that it is impermissible to base findings of obviousness upon his own expertise. Thankfully, the substantial competent evidence of record that has clearly been set forth by the teachings of the combined prior art references of Lechuga and Kurachi clearly set forth a proper *prima facie* case of obviousness . . ." See Examiner's Reply, Page 19. This is incorrect. Neither shows 100 hr dosing (a completely novel element), nor preventative use, as admitted by Examiner. Further, activity and monomer level cannot be presumed based on 300X greater particle size, as shown above.

## 4. DEFICIENCIES "OBVIATED BY THE TEACHINGS OF" LECHUGA OR KURACHI

The Examiner states on page 8 of the Examiner's Answer:

> Lechuga does not explicitly teach or disclose anticipatory methods of treating hemophilia, preventing bleeding associated with a hemophilic assault as stated in the instant claims, specify the treatment of hemophilia B, teach monomeric percentage of FIX, the step of "slowly maximally inhaling", or the "step" of" allowing said monomeric FIX to deposit in the deep lung tissue." These **deficiencies are obviated by the teachings of Lechuga or are obviated per the teachings of Kurachi**. (emphasis added).

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[1] See http://www.rcsb.org/pdb/explore/explore.do?structureId=1RFN.

[2] In fact, monomer content and lack of aggregation was assessed by SDS-PAGE and *uv* spectrometry (see Specification, ¶ 79, 83).

This is facially insufficient. Lechuga cannot "obviate" its own lack of teaching, and Kurachi only teaches that *in vivo* FIX is a monomer. Neither teaches the claimed preventative 100 hr dosing schedule, which was impossible before Applicants invention thereof.

5. **"NEXT LOGICAL STEP"**

Examiner states on page 9 of the Examiner's Answer that:

> Regarding the stated method of preventing hemophilic bleeding in advance of a hemophilic assault, because the composition taught by Lechuga has the **same components** as that claimed by Appellants and the treatment of the hemophilia is a consequence of the delivery of the active composition by inhalation and **ordinary skilled artisan would have arrived at the claimed method upon taking the inhalable FIX dry powders prepared by Lechuga onto the next logical step of administering said powder** to a hemophiliac to test the effectiveness of said powder in the treatment of hemophilic bleeding. (emphasis added).

This is facially insufficient. Lechuga does not teach the "same components" and even if it did, Examiner does not explain how the skilled artisan would arrive at the novel 100 hr preventative dosing regime, particularly where the 100 hr dosing regime was never before used in the art.[3] There is nothing in the cited art to suggest **changing** the dosage regime from what was used previously in the art, and Examiners' explanation thereof amounts to "taking the next logical step." Examiner fails to articulate any basis for concluding that the next logical step would be to use 100 hr dosing.

6. **"SAME PROPERTIES"**

Examiner also states on page 17:

> Finally concerning the observed sequestration effect and the claimed prophylactic property, administration of Lechuga's invented inhalable FIX dry powder formulations would **reasonably be expected to exhibit the same or substantially similar properties**, because Lechuga's invented inhalable FIX dry powder formulations comprise the same active agent, exhibit the required MMAD, preferably have a water content below 6% (i.e. this meets the limitation of a water content less than 10%), and have a FPF that overlaps significantly with the FPF required by Appellants'

[3] The prior art teaches that intravenous FIX leads to a high initial level of FIX, causing clotting complications. Inhaled FIX, in contrast, provides a very steady state level of FIX for more than 100 hrs, making it suitable for routine preventative use.

method (i.e. Lechuga teaches a FPF of 35-85% and Appellants' claims require a FPF of less than 3.3 microns of 50-1 00%).

Therefore, Examiner presumes that preventative and 100 hr dosing regimes would "reasonably be expected to exhibit the same or substantially similar properties" since the formulations are so similar. Applicant again notes that Lechuga only teaches a formulation, not a treatment. Examiner has assumed a particular method of use based on a similar formulation, but a **method of use is not a property of the formulation.**

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."[4] **How does 100 hr dosing "necessarily flow" from the formulation of Lechuga?** The Examiner's Answer does not even discuss 100 hr dosing. No answer is provided, because none is available. The dosing regime was **unknown** before Applicants invention.[5]

## 7. CONCLUSION

The claims cannot be obvious where the 100 hr dosing and preventative treatments are missing from the cited art, where no rational is provided for changing existing dosing regimes, and where both monomer and activity levels are presumed based on powder particle size 300 fold larger than a monomer, and where the Examiner has failed to rebut evidence of unexpected results.

If any questions or issues remain in the resolution of which the Board feels will be advanced by a conference with the Applicants' attorney, the Board is invited to contact the attorney at the number noted below. No fees are believed to be due for this submission. Howerver, the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-3420 (reference 31176282-004001 Valoir).

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[4] *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

[5] *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("Obviousness cannot be predicated on what is unknown.") (citing Spormann); *In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966) ("The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

Dated: July 25, 2008

Respectfully submitted,

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